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☐ 1. Document ID: US 6017880 A

L5: Entry 1 of 1 File: USPT Jan 25, 2000

US-PAT-NO: 6017880
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TITLE: Inhibition of retrovirus infection

DATE-ISSUED: January 25, 2000

See all claims: Group A "methods for inhibiting infection"; Group B "methods for treating infection"

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Eisenberg; Stephen	Boulder	CO		
Wahl; Sharon M.	Gaithersburg	MD		
Thompson; Robert C.	Boulder	CO		
Dripps; David J.	Niwot	CO		

US-CL-CURRENT: 514/12; 435/252.3, 435/320.1, 435/69.1, 514/2, 530/300, 530/324

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Terms	Documents
6017880.pn.	1

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Previous Page Next Page

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Dripps; David J.	Niwot	CO		

US-CL-CURRENT: 514/12; 435/252.3, 435/320.1, 435/69.1, 514/2, 530/300, 530/324

CLAIMS:

What is claimed is:

1. An in vitro method for inhibiting retrovirus infection of CD4.sup.+ cells in a composition containing said cells comprising contacting said composition with an amount of a secretory leukocyte protease inhibitor sufficient to inhibit retrovirus infection of said cells, wherein said secretory leukocyte protease inhibitor comprises the amino acid sequence of a naturally-occurring secretory leukocyte protease inhibitor or a substitution analog comprising the amino acid sequence (SEQ ID NO:4):

Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-
Tyr-Lys-Lys-Pro-Gln-Cys-Leu-R2
Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-Gly-Lys-Lys-
Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-Lys-Cys-Leu-
Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R8
Asp-Gly-Pro-Asn-Phe-Cys-Glu-R4
Gly-R6 -Lys-Arg-Asp-Leu-Lys-Cys-Cys-R5
Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-R7

wherein

R1 and R7 are the same or different and are selected from the group consisting of serine, alanine, or a substituted or unsubstituted amino acid residue:

R2, R3, R4, R5 and R6 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine: and

R8 and R9 are the same or different and are selected from the group consisting of

methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine.

2. The method according to claim 1, wherein the retrovirus is a human immunodeficiency deficiency virus (HIV).

3. The method according to claim 2, wherein the HIV is HIV-1.

4. The method of claim 1, wherein said secretory leukocyte protease inhibitor is used in combination with one or more antiviral or antibacterial agents.

5. The method of claim 1, wherein said substitution analog has phenylalanine at position R8.

6. The method of claim 1, wherein said substitution analog has glycine at position R2.

7. The method of claim 1, wherein said substitution analog has glycine at R8.

8. The method of claim 1, wherein said substitution analog has valine at position R8.

9. The method of claim 1, wherein said secretory leukocyte protease inhibitor is covalently-linked to polyethylene glycol.

10. The method of claim 1, wherein said cells are monocytes.

11. The method of claim 1, wherein said cells are T cells.

12. The method of claim 1, wherein each of R1 and R7 is a substituted or unsubstituted amino acid residue and R1 and R7 are the same or different.

13. A method for treating retrovirus infection comprising treating a patient with an amount of a secretory leukocyte protease inhibitor sufficient to inhibit retrovirus infection of CD4.sup.+ cells, wherein said secretory leukocyte protease inhibitor comprises the amino acid sequence of a naturally-occurring secretory leukocyte protease inhibitor or a substitution analog comprising the amino acid sequence (SEQ ID NO:4):

Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-
Tyr-Lys-Lys-Pro-Gln-Cys-Leu-R2
Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-Gly-Lys-Lys-
Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-Lys-Cys-Leu-
Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R8
Asp-Gly-Pro-Asn-Phe-Cys-Glu-R4
Gly-R6 -Lys-Arg-Asp-Leu-Lys-Cys-Cys-R5
Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-R7

wherein

R1 and R7 are the same or different and are selected from the group consisting of serine, alanine or a substituted or unsubstituted amino acid residue;

R2, R3, R4, R5 and R6 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R8 and R9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine.

14. The method according to claim 13, wherein the retrovirus is a human immunodeficiency virus (HIV).

15. The method according to claim 14, wherein the HIV is HIV-1.

16. The method of claim 13, wherein said secretory leukocyte protease inhibitor is administered intraperitoneally.

17. The method of claim 13, wherein said secretory leukocyte protease inhibitor is administered intravenously.

18. The method of claim 13, wherein said secretory leukocyte protease inhibitor is administered subcutaneously.

19. The method according to claim 13, wherein said substitution analog has phenylalanine at position R8.

20. The method according to claim 13, wherein said substitution analog has glycine at position R2.

21. The method according to claim 13, wherein said substitution analog has glycine at position R8.

22. The method according to claim 13, wherein said substitution analog has valine at position R8.

23. The method according to claim 13, further comprising administering at least one additional antiviral or antibacterial agent.

24. The method according to claim 13, wherein said secretory leukocyte protease inhibitor is covalently linked to polyethylene glycol.

25. The method of claim 13, wherein each of R1 and R7 is a substituted or unsubstituted amino acid residue and R1 and R7 are the same or different.

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☐ 1. Document ID: US 6132990 A

L6: Entry 1 of 1 File: USPT Oct 17, 2000

US-PAT-NO: 6132990
DOCUMENT-IDENTIFIER: US 6132990 A
**** See image for Certificate of Correction ****

TITLE: Recombinant methods for production of serine protease inhibitors and DNA sequences useful for same

DATE-ISSUED: October 17, 2000

Seeclaims 12, gachtwdoledp

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bandyopadhyay; Pradip K.	Boulder	CO		
Eisenberg; Stephen P.	Boulder	CO		
Stetler; Gary L.	Lafayette	CO		
Thompson; Robert C.	Boulder	CO		

US-CL-CURRENT: 435/69.2; 435/252.3, 435/252.31, 435/320.1, 435/69.7, 435/69.9, 514/12, 530/324, 536/23.4, 536/23.5

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Terms	Documents
6132990.pn.	1

Display Format: CIT Change Format

Previous Page Next Page

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Thompson; Robert C.	Boulder	CO		

US-CL-CURRENT: 435/69.2; 435/252.3, 435/252.31, 435/320.1, 435/69.7, 435/69.9, 514/12, 530/324, 536/23.4, 536/23.5

CLAIMS:

What is claimed is:

1. A purified and isolated mammalian serine protease inhibitor protein comprising at least 8 cysteine residues and the amino acid sequence:

Gln-Cys-R.sub.8 -R.sub.3 -R.sub.9 -Asn-Pro-Pro-Asn-Phe-Cys-Glu-R.sub.4 -Asp

wherein

R.sub.3 and R.sub.4 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine, and

wherein said protein has less than 107 amino acids and inhibits chymotrypsin and elastase.

2. A protease inhibitor protein of claim 1, comprising the amino acid sequence:

Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-Gly-
Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R8-R3-R9-Asn-Pro-Pro-
- Asn-Phe-Cys-Glu-R4-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-Cys-
- Cys-R5-Gly-R6-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala

---

wherein

R.sub.3, R.sub.4, R.sub.5, and R.sub.6, are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, leucine, glycine and arginine.

3. A protease inhibitor according to claim 2 wherein R.sub.3 is methionine.

4. A protease inhibitor according to claim 2 wherein R.sub.3 is arginine.

5. A protease inhibitor according to claim 2 wherein R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are methionine and R.sub.8 and R.sub.9 are leucine.

6. A protease inhibitor according to claim 2 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is valine.

7. A protease inhibitor according to claim 2 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is alanine.

8. A protease inhibitor according to claim 2 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is selected from the group consisting of phenylalanine, tyrosine and tryptophan.

9. The protease inhibitor protein of claim 1, comprising the amino acid sequence:

Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-Gly-
Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-Pro-
- Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-Cys-
- Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala.

---

10. The protease inhibitor protein of claim 1, wherein said protein is recombinantly produced.

11. A pharmaceutical composition comprising a serine protease inhibitor protein of claim 1.

12. A method of treating a serine protease-mediated condition comprising administering a serine protease inhibitor protein of claim 1.

13. An isolated or synthetic DNA sequence encoding a mammalian serine protease inhibitor protein comprising at least 8 cysteine residues and the amino acid sequence:

Gln-Cys-R.sub.8 -R.sub.3 -R.sub.9 -Asn-Pro-Pro-Asn-Phe-Cys-Glu-R.sub.4 -Asp

wherein

R.sub.3 and R.sub.4 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine, and

wherein said protein has no more than 107 amino acids and inhibits chymotrypsin and elastase.

14. A DNA sequence according to claim 13 encoding a serine protease inhibitor protein having the amino acid sequence:

Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-Gly-
Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R8-R3-R9-Asn-Pro-Pro-
- Asn-Phe-Cys-Glu-R4-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-Cys-
- Cys-R5-Gly-R6-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala

---

wherein

R.sub.3, R.sub.4, R.sub.5, and R.sub.6, are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, leucine, glycine and arginine.

15. A DNA sequence according to claim 14 wherein R.sub.3 is methionine.

16. A DNA sequence according to claim 14 wherein R.sub.3 is arginine.

17. A DNA sequence according to claim 14 wherein R.sub.3, R.sub.4, R.sub.5, and R.sub.6 are methionine and R.sub.8 and R.sub.9 are leucine.

18. A DNA sequence according to claim 14 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is valine.

19. A DNA sequence according to claim 14 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is selected from the group consisting of phenylalanine, tyrosine and tryptophan.

20. A DNA sequence according to claim 14 wherein one or more of R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 and R.sub.9 is alanine.

21. The DNA sequence of claim 13 which encodes a serine protease inhibitor protein having the amino acid sequence:

Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-Gly-
Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-Pro-
- Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-Cys-
- Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala.

---

22. The DNA sequence of claim 21 which has the nucleotide sequence:

CTG GAT CCT GTT GAC ACC CCA ACA CCA ACA AGG AGG AAG CCT GGG
AAG TGC CCA GTG ACT TAT GGC CAA TGT TTG ATG CTT AAC CCC CCC
- AAT TTC TGT GAG ATG GAT GGC CAG TGC AAG CGT GAC TTG AAG TGT
- TGC ATG GGC ATG TGT GGG AAA TCC TGC GTT TCC CCT GTG AAA GCT.

23. A synthetic DNA sequence encoding a serine protease inhibitor protein possessing serine protease inhibitor activity and having the following amino acid sequence:

R.sub.1 -Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-Ser-
- Ala-Gln-Cys-Leu-R.sub.2 -Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-

- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R.sub.8 -R.sub.3 -R.sub.9 -Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-R.sub.4 -Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-R.sub.5 -Gly-R.sub.6 -Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-R.sub.7,

or an inhibitory truncation analog thereof, wherein

R.sub.1 and R.sub.7 are the same or different and are selected from the group consisting of serine, alanine or a substituted or an unsubstituted amino acid residue;

R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine.

24. A DNA sequence according to claim 23, wherein R.sub.2 and R.sub.3 are methionine.

25. A DNA sequence according to claim 23, wherein R.sub.2 and R.sub.3 are arginine.

26. A DNA sequence according to claim 23, wherein R.sub.2 is arginine and R.sub.3 is methionine.

27. A DNA sequence according to claim 23, wherein R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are methionine and R.sub.8 and R.sub.9 are leucine.

28. A DNA sequence according to claim 23, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is valine.

29. A DNA sequence according to claim 23, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is selected from the group consisting of phenylalanine, tyrosine and tryptophan.

30. A DNA sequence according to claim 23, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is alanine.

31. A DNA sequence according to claim 23, wherein one or more of R2, R3, R4, R5, R6, R8 or R9 is selected from the group consisting of lysine or arginine.

32. A DNA sequence according to claim 23, wherein the amino acid at position 72 is substituted with an amino acid selected from the group consisting of phenylalanine, arginine and lysine.

33. A DNA sequence according to claim 23, encoding a serine protease inhibitor comprising the amino acid sequence:

Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-Ser-
Ala-Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

---

34. A synthetic DNA sequence according to claim 23, comprising:

5'- AGC GGT AAA AGC TTC AAA GCT GGC GTA TGC CCG CCG AAA AAA TCC GCG CAG
- TGT CTG CGG TAC AAA AAA CCG GAA TGC CAG TCC GAC TGG CAG TGC CCG
GGT
- AAA AAA CGT TGT TGC CCG GAC ACC TGC GGC ATC AAA TGC CTG GAT CCG
GTT
- GAT ACC CCG AAC CCG ACT CGT CGA AAA CCG GGT AAA TGC CCG GTA ACC
TAT
- GGC CAG TGT CTG ATG CTG AAC CCG CCG AAC TTC TGC GAA ATG GAC GGC
CAG
- TGT AAA CGA GAT CTG AAA TGC TGT ATG GGT ATG TGC GGC AAA TCT TGT
GTT
- TCC CCG GTA AAA GCA TAA -3'

---

35. A DNA sequence according to claim 23, encoding a serine protease inhibitor analog comprising the amino acid sequence:

Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

---

36. A DNA sequence according to claim 23, encoding a serine protease inhibitor analog comprising the amino acid sequence:

Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-

- Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-
- Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-
- Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala.

---

37. A DNA sequence according to claim 23, encoding a serine protease inhibitor analog comprising the amino acid sequence:

Arg-Lys-Pro-
- Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-
- Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-
- Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-
- Ala.

---

38. A DNA sequence according to claim 23, further comprising a DNA sequence encoding a secretory leader sequence at the 5' end of the DNA sequence.

39. An isolated DNA sequence comprising a coding region for a serine protease inhibitor protein possessing serine protease inhibitor activity and having the following amino acid sequence or a naturally occuring DNA sequence isolated from a human genomic or cDNA library and encoding a protein possessing serine protease inhibitor activity having no more than 107 amino acids and exhibiting substantial homology to the following amino acid sequence:

Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-Ser-
Ala-Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

---

40. A DNA sequence according to claim 39, encoding a serine protease inhibitor comprising the amino acid sequence:

Met-Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-
Ser-Ala-Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-
- Trp-Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-
- IIe-Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-
- Lys-Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-
- Asn-Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-
- Leu-Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-
- Val-Lys-Ala.

---

41. A DNA sequence according to claim 39, wherein said sequence is:

```
AGC GGT AAA AGC TTC AAA GCT GGC GTA TGC CCG CCG AAA AAA TCC GCG CAG
TGT CTG CGG TAC AAA AAA CCG GAA TGC CAG TCC GAC TGG CAG TGC CCG GGT
  - AAA AAA CGT TGT TGC CCG GAC ACC TGC GGC ATC AAA TGC CTG GAT CCG GTT
  - GAT ACC CCG AAC CCG ACT CGT CGA AAA CCG GGT AAA TGC CCG GTA ACC TAT
  - GGC CAG TGT CTG ATG CTG AAC CCG CCG AAC TTC TGC GAA ATG GAC GGC CAG
  - TGT AAA CGA GAT CTG AAA TGC TGT ATG GGT ATG TGC GGC AAA TCT TGT GTT
  - TCC CCG GTA AAA GCA TAA -3'.
```

42. A DNA sequence according to claim 39, encoding a serine protease inhibitor analog comprising the amino acid sequence:

```
    Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
  - Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
  - Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
  - Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
  - Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
  - Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
  - Lys-Ala.
```

43. A DNA sequence according to claim 39, encoding a serine protease inhibitor analog comprising the amino acid sequence:

```
                  Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-
  - Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-
  - Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-
  - Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-Ala.
```

44. A DNA sequence according to claim 39, encoding a serine protease inhibitor analog comprising the amino acid sequence:

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                                                    Arg-Lys-Pro-
  - Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-
  - Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-
  - Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-
  - Ala.
```

45. A DNA sequence according to claim 39, wherein said DNA sequence is a cDNA sequence.

46. A DNA sequence according to claim 39, wherein said DNA sequence is a genomic sequence.

47. A DNA sequence according to claim 39, further comprising a secretory leader sequence at the 5' end of the DNA sequence.

48. A recombinant vector for transformation of a host cell which comprises the DNA sequence of any of claims 13, 21, or 14.

49. The recombinant vector of claim 48 which is an expression vector.

50. The recombinant vector of claim 49 which further comprises a DNA sequence encoding a secretory leader sequence.

51. A host cell transformed with the recombinant vector of claim 48.

52. A host cell transformed or transfected with a DNA sequence according to claim 23.

53. A host cell according to claim 52, wherein said host cell is a microorganism.

54. A host cell according to claim 53, wherein said microorganism is selected from the genera in the group consisting of Escherichia, Bacillus and Saccharomyces.

55. A host cell transformed or transfected with a DNA sequence according to claim 39.

56. A host cell according to claim 55, wherein said host cell is a microorganism.

57. A host cell according to claim 56, wherein said microorganism is selected from genera in the group consisting of Escherichia, Bacillus and Saccharomyces.

58. A method for producing a recombinant serine protease inhibitor protein which inhibits chymotrypsin and elastase, said method comprising:

(a) culturing a host cell transformed or transfected with a DNA sequence encoding a mammalian serine protease inhibitor protein comprising at least 8 cysteine residues and the amino acid sequence:

Gln-Cys-R.sub.8 -R.sub.3 -R.sub.9 -Asn-Pro-Pro-Asn-Phe-Cys-Glu-R.sub.4 -Asp

wherein

R.sub.3 and R.sub.4 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine, wherein the serine protease inhibitor protein has no more than 107 amino acids, under conditions suitable for expression of the serine protease inhibitor protein, and;

(b) harvesting the serine protease inhibitor protein.

59. A method for the recombinant DNA synthesis of a serine protease inhibitor comprising the amino acid sequence:

R.sub.1 -Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-Ser-
- Ala-Gln-Cys-Leu-R.sub.2 -Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-R.sub.8 -R.sub.3 -R.sub.9 -Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-R.sub.4 -Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-

- Lys-Cys-Cys-R.sub.5 -Gly-R.sub.6 -Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-R.sub.7,

---

or an inhibitory truncation analog thereof, wherein

R.sub.1 and R.sub.7 are the same or different and are selected from the group consisting of serine, alanine or a substituted or an unsubstituted amino acid residue;

R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine; and

R.sub.8 and R.sub.9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine, leucine and arginine;

said method comprising culturing a host cell, which is transformed or transfected with a DNA sequence encoding said serine protease inhibitor or inhibitory truncation analog thereof under conditions suitable for expression of the inhibitor or inhibitory truncation analog, and harvesting the expressed serine protease inhibitor or inhibitory truncation analog.

60. A method according to claim 59, wherein R.sub.2 and R.sub.3 are methionine.

61. A method according to claim 59, wherein R.sub.2 and R.sub.3 are arginine.

62. A method according to claim 59, wherein R.sub.2 is arginine and R.sub.3 is methionine.

63. A method according to claim 59, wherein R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are methionine and R.sub.8 and R.sub.9 are leucine.

64. A method according to claim 59, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is valine.

65. A method according to claim 59, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is alanine.

66. A method according to claim 59, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is selected from a group consisting of phenylalanine, tyrosine and tryptophan.

67. A method according to claim 59, wherein one or more of R.sub.2, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.8 or R.sub.9 is selected from the group consisting of lysine or arginine.

68. A method according to claim 59, wherein said DNA sequence encodes a serine protease inhibitor in which the amino acid at position 72 is substituted with an amino acid selected from the group consisting of phenylalanine, arginine and lysine.

69. A method according to claim 59, wherein said DNA sequence encodes a serine protease inhibitor comprising the amino acid sequence:

Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-Pro-Lys-Lys-Ser-
Ala-Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-Ile-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-

- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

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70. A method according to claim 59, wherein said DNA sequence encodes a serine protease inhibitor analog comprising the amino acid sequence:

Gln-Cys-Leu-Arg-Tyr-Lys-Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-
- Gln-Cys-Pro-Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-IIe-
- Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

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71. A method according to claim 59, wherein said DNA sequence encodes a serine protease inhibitor analog comprising the amino acid sequence:

Val-Asp-Thr-Pro-Asn-Pro-Thr-Arg-Arg-Lys-Pro-
- Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-
- Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-Lys-
- Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-Lys-
- Ala.

---

72. A method according to claim 59, wherein said DNA sequence encodes a serine protease inhibitor analog comprising the amino acid sequence:

Arg-Lys-
- Pro-Gly-Lys-Cys-Pro-Val-Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-
- Pro-Pro-Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-Asp-Leu-
- Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-Ser-Cys-Val-Ser-Pro-Val-
- Lys-Ala.

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73. A method according to claim 59, wherein said DNA sequence is a synthetic sequence.

74. A method according to claim 59, wherein said DNA sequence is a natural DNA sequence.

75. A method according to claim 59, further comprising refolding the serine protease inhibitor expressed by a bacterial host cell.

76. A method according to claim 59, further comprising purifying the serine protease inhibitor.

77. A method according to claim 59, further comprising refolding the serine protease inhibitor expressed by a bacterial host cell subsequent to said purification.

78. A method according to claim 59, further comprising refolding the serine protease inhibitor expressed by a bacterial host cell prior to said purification.

79. A method according to claim 59, wherein said host cell is a microorganism.

80. A method according to claim 79, wherein said microorganism is selected from genera in the group consisting of Escherichia, Bacillus, and Saccharomyces.

81. A method according to claim 79, wherein said microorganism is Escherichia coli.

82. A method according to claim 79, wherein said microorganism is Saccharomyces cerevisiae.

83. A method for producing a recombinant serine protease inhibitor protein which inhibits chymotrypsin and elastase, said method comprising:

(a) culturing a host cell transformed or transfected with a recombinant vector according to claim 64 under conditions suitable for expression of the serine protease inhibitor protein; and

(b) harvesting the serine protease inhibitor protein.